

CLAIMS

What is claimed is:

1. A parkin-associated complex, comprising parkin, hSel-10, and cullin-1.
2. The complex of claim 1, which has ubiquitin ligase activity.
3. The complex of claim 1, further comprising cyclin E.
4. The complex of claim 1, wherein parkin comprises the carboxyl terminus (residues 76-465) of parkin.
5. The complex of claim 4, wherein parkin comprises two RING finger domains.
6. The complex of claim 5, wherein parkin comprises amino acid residue T240.
7. A method for promoting ubiquitination of cyclin E in a post-mitotic neuron, comprising increasing activity of a parkin-associated complex in the neuron, wherein the parkin-associated complex comprises parkin, hSel-10, and cullin-1.
8. The method of claim 7, wherein the neuron is a dopamine neuron.
9. The method of claim 7, wherein activity of the parkin-associated complex is increased in the neuron by increasing the level of the complex in the neuron.
10. The method of claim 9, wherein activity of the parkin-associated complex is increased in the neuron by contacting the neuron with a parkin-associated agent, wherein the parkin-associated agent is selected from the group consisting of a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity.

11. The method of claim 7, wherein the ubiquitination of cyclin E is promoted *in vitro*.

12. The method of claim 7, wherein the ubiquitination of cyclin E is promoted *in vivo* in a subject.

13. The method of claim 12, wherein the ubiquitination of cyclin E is promoted *in vivo* in a subject by administering a parkin-associated agent to the subject.

14. The method of claim 13, wherein the subject is a human.

15. The method of claim 14, wherein the human has neurodegeneration.

16. The method of claim 15, wherein the neurodegeneration is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, Huntington's chorea, multiple sclerosis, myasthenia gravis, Parkinson's disease, and Pick's disease.

17. The method of claim 16, wherein the neurodegeneration is sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease.

18. The method of claim 15, wherein the neurodegeneration is associated with glutamate excitotoxicity.

19. The method of claim 13, wherein parkin is administered to the subject orally, intradermally, intramuscularly, intraperitoneally, intravenously, or subcutaneously.

20. A therapeutic composition, comprising:

- (a) a nucleic acid encoding a parkin-associated agent;
- (b) a lentiviral vector; and
- (c) optionally, a pharmaceutically-acceptable carrier;

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wherein the parkin-associated agent is selected from the group consisting of a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity.

5 21. A method for treating neurodegeneration in a subject in need of treatment, comprising administering to the subject the therapeutic composition of claim 20, in an amount effective to treat the neurodegeneration in the subject.

10 22. The method of claim 21, wherein the neurodegeneration is sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease.

 23. Use of the therapeutic composition of claim 20 in an animal model of Parkinson's disease.

15 24. A method for identifying an agent which interacts with a parkin-associated complex, comprising the steps of:

 (a) contacting a candidate agent with the complex, in the presence of cyclin E; and

 (b) assessing the ability of the candidate agent to enhance interaction between the
20 complex and cyclin E;

 wherein the parkin-associated complex comprises parkin, hSel-10, and cullin-1.

 25. The method of claim 24, further comprising the steps of:

 (c) contacting the candidate agent with at least one post-mitotic neuron containing
25 cyclin E; and

 (d) determining if the agent has an effect on a cyclin-E-associated biological event in the at least one neuron.

30 26. The method of claim 25, wherein the cyclin-E-associated biological event is selected from the group consisting of accumulation of cyclin E, ubiquitination of cyclin E, apoptosis, and cyclin-E-associated neurodegeneration.

27. The agent identified by the method of claim 24.

28. The agent identified by the method of claim 25.

5 29. A method for protecting at least one post-mitotic neuron from excitotoxicity, comprising contacting the at least one neuron with an amount of the agent of claim 28 effective to protect the at least one neuron from excitotoxicity.

30. The method of claim 29, wherein the neuron is a dopamine neuron.

10 31. A method for treating or preventing neurodegeneration in a subject, comprising administering to the subject an amount of the agent of claim 28 effective to treat or prevent the neurodegeneration in the subject.

15 32. The method of claim 31, wherein the neurodegeneration is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, Huntington's chorea, multiple sclerosis, myasthenia gravis, Parkinson's disease, and Pick's disease.

20 33. The method of claim 32, wherein the neurodegeneration is sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease.

34. The method of claim 31, wherein the neurodegeneration is associated with glutamate excitotoxicity.

25 35. A method for decreasing cyclin E in at least one post-mitotic neuron, comprising contacting the at least one neuron with a parkin-associated agent, in an amount effective to decrease cyclin E in the neuron, wherein the parkin-associated agent is selected from the group consisting of a parkin protein, a parkin mimetic, a modulator of parkin
30 expression, and a modulator of parkin activity.

36. The method of claim 35, wherein cyclin E is decreased in the at least one neuron by decreasing the level of cyclin E in the neuron or by decreasing accumulation of cyclin E in the neuron.

5 37. The method of claim 35, wherein the neuron is selected from the group consisting of a cerebellar granule neuron, a cortical neuron, and a substantia nigra neuron.

38. The method of claim 35, wherein the neuron is damaged.

10 39. The method of claim 38, wherein the damage results from excitotoxicity.

40. The method of claim 35, wherein the contacting is effected *in vitro*.

41. The method of claim 35, wherein the contacting is effected *in vivo* in a subject.

15 42. The method of claim 41, wherein the contacting is effected *in vivo* in a subject by administering the parkin-associated agent to the subject.

43. The method of claim 42, wherein the subject is a human.

20 44. The method of claim 43, wherein the human has neurodegeneration.

45. A method for protecting at least one post-mitotic neuron from excitotoxicity, comprising contacting the at least one neuron with a parkin-associated agent, in an amount
25 effective to protect the neuron from excitotoxicity, wherein the parkin-associated agent is selected from the group consisting of a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity.

46. The method of claim 45, wherein the neuron is a dopamine neuron.

30 47. The method of claim 45, wherein the neuron is a cerebellar granule cell.

48. The method of claim 45, wherein the excitotoxicity is glutamate excitotoxicity.

49. The method of claim 48, wherein the glutamate excitotoxicity is kainate-mediated excitotoxicity.

50. The method of claim 45, wherein protection from excitotoxicity results in protection from apoptosis.

51. The method of claim 45, wherein the contacting is effected *in vitro*.

52. The method of claim 45, wherein the contacting is effected *in vivo* in a subject.

53. The method of claim 52, wherein the contacting is effected *in vivo* in a subject by administering the parkin-associated agent to the subject.

54. Use of a parkin-associated agent to protect a post-mitotic neuron from excitotoxicity, wherein the neuron is contacted with an amount of parkin-associated agent effective to protect the neuron from excitotoxicity, and wherein the parkin-associated agent is selected from the group consisting of a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity.

55. A method for determining whether a subject has neurodegeneration, comprising assaying a diagnostic sample of the subject for cyclin E, wherein detection of a cyclin E level elevated above normal is diagnostic of neurodegeneration in the subject.

56. The method of claim 55, wherein the neurodegeneration is sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease.

57. The method of claim 55, wherein the diagnostic sample is a sample from the frontal cortex, midbrain, or substantia nigra of the subject.

58. The method of claim 55, wherein the diagnostic sample is assayed using an agent reactive with cyclin E.

59. The method of claim 58, wherein the agent is labeled with a detectable
5 marker.

60. The method of claim 58, wherein the agent is an antibody.

61. The method of claim 55, wherein the diagnostic sample is assayed using at
10 least one nucleic acid probe which hybridizes to nucleic acid encoding cyclin E.

62. The method of claim 61, wherein the nucleic acid probe is labeled with a detectable marker.

63. A method for assessing the efficacy of therapy to treat neurodegeneration in a
15 subject who has undergone or is undergoing treatment for neurodegeneration, comprising
assaying a diagnostic sample of the subject for cyclin E, wherein a normal level of cyclin E in
the diagnostic sample is indicative of successful therapy to treat neurodegeneration, and a
level of cyclin E elevated above normal in the diagnostic sample is indicative of a need to
20 continue therapy to treat neurodegeneration.

64. A method for assessing the prognosis of a subject who has neurodegeneration,
comprising assaying a diagnostic sample of the subject for cyclin E, wherein the subject's
prognosis improves with a decreased level of cyclin E in the diagnostic sample, and the
25 subject's prognosis worsens with an increased level of cyclin E in the diagnostic sample.

65. A kit for use in detecting neurodegeneration, comprising:

- (a) a cyclin-E-specific agent; and
- (b) reagents suitable for detecting cyclin E;

30 wherein the cyclin-E-specific agent is selected from the group consisting of an agent
reactive with cyclin E and a nucleic acid probe which hybridizes to nucleic acid encoding
cyclin E.

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66. The kit of claim 65, wherein the cyclin-E-specific agent is labeled with a detectable marker.

5 67. The kit of claim 65, wherein the agent reactive with cyclin E is an antibody.